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EXAMINER

MYERS, CARLA J

ART UNIT	PAPER NUMBER
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1634

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/590,823	Applicant(s) SHIOZAWA ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 1-6 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 August 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/10/09, 1/18/07, 8/25/06</u> . | 6) <input checked="" type="checkbox"/> Other: <u>translation of Takami et al Nov 2003</u> . |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II, claims 7-10 in the reply filed on September 23, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Claims 1-10 are pending. Claims 7-10 have been examined herein. Claims 1-6 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Interpretation

3. It is noted that claims 7-10 recite the phrase "strongly methylated." This phrase is defined at page 36 of the specification as referring to "the state in which 70% or greater than 70% of the CpG sequences in the polynucleotide are methylated."

Claim Rejections - 35 USC § 112 second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-10 are indefinite. The claims are drawn to a method for determining development of RA or the likelihood of developing RA. The claims recite a final step of comparing a methylation state of a DR3 gene promoter region or confirming that the DR3 gene promoter region is strongly methylated. The claims do not, however, recite

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an active process of determining development of RA or the likelihood of developing RA. It is hereby unclear as to whether the claims are intended to be limited to a method which only compares the methylation state of the DR3 gene promoter region or which confirms that the DR3 gene promoter region is strongly methylated or if the claims are intended to be limited to methods which determine development of RA or the likelihood of developing RA. In the later case, the claims omit the essential process step of determining development of RA or the likelihood of developing RA. See MPEP § 2172.01.

Claims 7-10 are also indefinite over the acronym of "RA." This acronym has many different meanings in the art, including refractory anemia, regulatory affairs, and radon. However, the claims do not set forth a particular meaning for the acronym. Accordingly, one cannot determine the meets and bounds of the claimed subject matter. This rejection may be overcome by amendment of claim 7 to recite "method for determining development of rheumatoid arthritis (RA)."

Claim 8 is indefinite over the recitation of "the methylation state of the DR3 gene promoter A regions" because this phrase lacks proper antecedent basis. While the claim previously refers to determining the methylation state of the DR3 gene promoter, the claim does not previously refer to the DR3 gene promoter A regions. Further, while the specification provides examples of what may be encompassed by the promoter A region, the specification does not provide a complete and limiting definition for what may be encompassed by "the promoter A regions." This phrase is also not clearly defined in

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the claims or art. Accordingly, one cannot determine the meets and bounds of the claimed subject matter.

Claim 10 is indefinite over the recitation of "DR3 promoter region originating in the peripheral blood lymphocytes" (claim 10, line 7). The claim previously refers to two different sources of peripheral blood lymphocytes – the peripheral blood lymphocytes recited in claim 7, line 4 and the peripheral blood lymphocytes of healthy subjects recited in claim 10, line 2. It is unclear as to whether the peripheral blood lymphocytes recited in claim 7 line 4 are the same as or different from peripheral blood lymphocytes recited in claim 10, line 2, and if the peripheral blood lymphocytes are different, it is unclear as to which lymphocytes are being referred to in claim 10, line 7.

Claim Rejections - 35 USC § 112, first paragraph - Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining if a human subject is at an increased risk for developing rheumatoid arthritis (RA) comprising providing a sample of synovial cells or synovial infiltrating cells from a human subject, determining the methylation status of a DR3 gene promoter region obtained from the synovial cells or synovial infiltrating cells, wherein the DR3 gene promoter region consists of the nucleotides upstream of the translation initiation point to nucleotide -180, comparing the methylation status of the DR3 gene promoter region from the synovial cells or synovial

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infiltrating cells of the human subject to the methylation status of the DR3 gene promoter region obtained from peripheral blood lymphocytes of the human subject or peripheral blood lymphocytes obtained from healthy human controls, and determining that the human subject is at an increased risk for developing rheumatoid arthritis if the DR3 gene promoter region obtained from the synovial cells or synovial infiltrating cells is strongly methylated as compared to the DR3 gene promoter obtained from the peripheral blood lymphocytes,

does not reasonably provide enablement for methods which determine the development of RA or likelihood of developing RA in any non-human subject, methods which determine the development of RA or likelihood of developing RA by assaying for the methylation status for any single CpG in the DR3 gene promoter or which analyze any region of the DR3 gene promoter, or methods which determine the development of RA or likelihood of developing RA by confirming by any means or methodology that the DR3 gene promoter obtained from synovial cells is strongly methylated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance

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presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for determining the development of RA or likelihood of developing RA comprising comparing a methylation state of a DR3 gene promoter region obtained from synovial cells or synovial infiltrating lymphocytes with a methylation state of a DR3 gene promoter region obtained from peripheral blood lymphocytes, or confirming that the DR3 gene promoter region obtained from the synovial cells is strongly methylated.

The claims are inclusive of methods which determine the development of RA or likelihood of developing RA in any subject, including such diverse non-human subjects as rats, dogs, horses, pigs, pandas etc.

The claims encompass methods in which the methylation status of a single CpG in the DR3 gene promoter is determined or in which the methylation status of any portion of the promoter region is determined in order to assess development of RA.

The claims also encompass methods in which methylation of the DR3 gene promoter is confirmed by any means or by using any methodology, including methods which infer methylation status by assaying for DR3 gene expression levels or by assaying for promoter activity..

Nature of the Invention

The claims encompass determining the development of RA or likelihood of developing RA by assaying for the methylation status of the DR3 gene promoter. The

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invention is in a class of inventions which the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the results of a study of the methylation status of regions A, B and C of the DR3 gene promoter in cell samples from human subjects. Region A consists of nucleotides 1-173 of SEQ ID NO: 1, region B consists of nucleotides 174 to 373 of SEQ ID NO: 1, and region C consists of nucleotides 374 to 592 of SEQ ID NO: 1 (page 19). Relative to the translation initiation start point, region B consists of nucleotides -380 to -180 and region C consists of the sequences upstream from the start site to position -180 (page 22).

The methylation status of the above defined regions A, B and C was determined in samples obtained from synovial cells of RA patients, and in peripheral blood lymphocytes of RA patients and healthy controls. The specification (page 42) states that "all of the CpG sequences in A region were methylated in all samples. In B region, all samples had both unmethylated and methylated CpG sequences. In C region (promoter region of DR3 gene), unmethylated and methylated CpG sequences coexisted only in samples originating in the synovial cells of RA patients, and all of the CpG sequences were unmethylated in the other samples." Thus, the specification teaches that the methylation status of regions A and B in synovial cells as compared to peripheral blood lymphocyte cells was not correlated with RA (see also page 45). However, region C of the DR3 promoter was more highly methylated in synovial cells from RA patients as

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compared to peripheral blood lymphocyte cells from RA and normal healthy subjects.

Further, region C of the DR3 gene promoter was highly methylated in synovial cells obtained from human subjects with osteoarthritis (OA) - see Figures 6 and 12.

The results presented in Figures 5A and 5B indicate that region C is more highly methylated in synovial cells and synovial infiltrating lymphocytes of RA patients as compared to lymphocytes in joint fluid of RA patients (see also pages 43-44). Regions A and B did not show a difference in methylation status in samples of synovial cells and synovial infiltrating lymphocytes and lymphocytes from joint fluid of RA patients (page 43).

The Predictability or Unpredictability of the Art :

The art of determining an association between methylation status and the occurrence of a phenotype, such as RA, is highly unpredictable. The findings regarding the methylation status of one region of a promoter or gene cannot necessarily be extrapolated to other regions of a promoter or gene. In the present situation, the claims encompass analyzing any single CpG or any combination of any CpGs in any region of the DR3 gene promoter. However, the teachings in the specification clearly indicate that regions "A" (nucleotides 1-173 of SEQ ID NO: 1) and "B" (nucleotides 174 to 373 of SEQ ID NO: 1) did not show a difference in their methylation status in samples obtained from synovial cells of RA patients, peripheral blood lymphocytes of RA patients, or peripheral blood lymphocytes of normal, healthy subjects. Thus, it is highly unpredictable as to how the methylation status of any single CpG or any combination of CpGs in regions "A" or "B" could be determined as diagnostic of the development of RA.

It is also unpredictable as to whether the analysis of a single CpG in region "C" could be assayed for its methylation status as diagnostic of the development of RA. The findings in the specification indicate that it is the combination of CpGs in region C that when analyzed together are found to be more strongly methylated in synovial cells and synovial infiltrating lymphocytes of RA patients. In many RA patients, there are a number of individual CpGs which are not methylated and thereby when analyzed alone, their methylation status would not be indicative of RA (see Figures 8 and 12).

It is also unpredictable as to whether methylation status of the C region can be used to diagnose RA per se. The findings in the specification indicate that region C is also hypermethylated in synovial cells of OA patients (Figures 6 and 12). The specification does not teach that there is a difference in the level of methylation of region C in RA subjects as compared to OA subjects. Since hypermethylation of region C also occurs in samples obtained from synovial cells of OA subjects, the presence of hypermethylation of region C in synovial cells is not indicative of the development of RA alone, but rather is only indicative of an increased risk of developing RA.

Moreover, the present claims are inclusive of methods in which development of RA is determined in any non-human subject. However, the ability to extrapolate methylation status results from one animal to other animals is highly unpredictable. There is no information provided in the specification which would indicate that a change in methylation status of DR3 promoter sequences occurs in a representative number of, such as mice, dogs, goats, horses, pandas etc, and is indicative of development of RA.

The unpredictability of extrapolating the methylation status results obtained in humans to non-human organisms is supported by the teachings of Ehrlich et al. (Oncogene 2002. 21: 5400-5413). Ehrlich reports that there is considerable differences in the amounts and distribution of DNA methylation among different vertebrate tissues because DNA methylation is not only species-specific but also tissue-specific (p. 5400 last paragraph). Therefore, the findings regarding an association between methylation status in humans cannot be extrapolated to any other species predictably. Because the distribution of DNA methylation varies between species it is not predictable that the same methylation status differences observed in one species is correlative in another species. Erlich (page 5401) also teaches that it is important to determine the methylation status in "uncultured cell populations whenever possible because of the frequent changes in DNA methylation that occur upon cell culture."

The lack of a clear structure – function relationship between DR3 methylation and RA, further compounds the unpredictability of extrapolating results obtained from humans to other organisms. In view of the variability in gene expression levels and thereby the expected variability in methylation patterns between organisms and the lack of a structure-function relationship between methylation of the DR3 gene promoter and the occurrence of RA, insufficient information is provided in the specification to establish that any results obtained in the specification regarding DR3 methylation in humans can be extrapolated to a representative number of diverse non-human organisms.

The claims encompass methods in which strong methylation of the DR3 gene promoter is confirmed by any method or means. For instance, the claims encompass

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methods which confirm the methylation status of the DR3 gene promoter by performing assays that screen for a change in the activity of DR3 protein, or a change in a biological activity or biological characteristic (cell morphology etc) that is associated with DR3 expression or activity. However, there is no specific disclosure in the specification of a particular assay that can be used to indirectly confirm that the DR3 gene promoter is strongly methylated. It is highly unpredictable as to whether strong methylation of the DR3 gene promoter can be inferred by such assays as indicative of a RA. The level of DR3 mRNA or protein, or protein activity is not necessarily reflective of the occurrence of methylation status since a multitude of other factors may effect gene expression other than epigenetic silencing. For example, mutations in the promoter region may result in a decrease in mRNA or protein levels. Changes in cellular transcription factors may also alter transcription or translation of the DR3 gene, and thereby the level of DR3 mRNA or protein.

The teachings in the prior art support the unpredictability of inferring methylation status by, for example, assaying for gene expression. For example, Muller-Tidow (FEBS Letters. 2001. 490: 75-78) states that "The role of genomic CpG methylation in the regulation of gene expression is highly controversial" (page 77, col. 2). Muller-Tidow teaches that CpG methylation patterns of the human cyclin A1 promoter in human organs do not correlate with cyclin A1 gene expression in vivo (page 77, col. 2). The teachings of Sato et al (Arthritis and Rheumatism. Sept. 2003. S458, Abstract 1146) also support this unpredictability. Sato teaches the existence of a soluble splice variant of the DR3 gene that does not contain exon 7, which encodes for the transmembrane

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domain. Sato teaches that the expression of the splice variant was significantly reduced in PBMCs from patients with RA as compared to healthy controls. It is stated that the presence of reduced quantities of the soluble splice variant of DR3 may be important in the pathogenesis of RA. However, the present specification does not provide any information regarding the relationship between methylation status and the quantity of the soluble splice variant form of DR3, such that one could detect the quantity of this splice variant in PBMCs and synovial cells or synovial infiltrating lymphocytes as indicative of the methylation status of the DR3 gene promoter. It is thereby highly unpredictable as to whether the quantity of DR3 expression can be detected to thereby infer and confirm the methylation state of the DR3 gene promoter.

Quantity of Experimentation and Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify additional animals whose DR3 methylation status is correlated with RA. The specification does not teach the existence of homologues of DR3 nucleic acids in a representative number of non-human organisms. There is also no information provided regarding the functional activity of DR3 nucleic acids in RA in a representative number of diverse organisms which would allow one to conclude that methylation of DR3 promoter sequences have a similar functional role in contributing to the occurrence of RA in a representative number of non-human organisms.

The specification does not provide sufficient guidance as to how to use the methylation status of sequences upstream of position -180 in the promoter region of the

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DR3 gene to determine the development of RA. The teachings in the specification indicate that region "A" of the DR3 gene promoter is methylated in healthy PBMCs and in PBMCs and synovial cells of RA patients, as well as in synovial cells of osteoarthritis patients. The teachings in the specification also indicate that region "B" of the DR3 gene promoter includes both methylated and unmethylated CpGs in healthy PBMCs and in PBMCs and synovial cells of RA patients, as well as in synovial cells of osteoarthritis patients. There are no clear teachings in the specification as to how to use the methylation status of such regions to determine the development of RA. The specification also does not provide any information regarding the methylation status of promoter sequences upstream of position -553 (i.e., upstream of region "A") of the DR3 promoter and thereby does not provide any guidance for how to determine the development of RA by analyzing the methylation status of sequences in the promoter region upstream of nucleotide position -553.

Extensive experimentation would be required to identify additional organisms and regions of the DR3 gene promoter which show a change in their methylation status in association with the occurrence of RA. While methods for determining CpG methylation status are known in the art, such methods provide only the general guidelines that allow researchers to randomly determine if particular CpGs or regions of a gene containing CpGs are methylated. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional organisms

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and particular CpGs in which an altered CpG methylation status will be correlated with RA.

Working Examples

The specification provides a working example establishing that human synovial cells and synovial infiltrating lymphocytes of RA patients show an increase in frequency of methylation of a region of the DR3 gene promoter that consists of nucleotides -180 to the translation initiation site (region "C") as compared to this region in peripheral blood lymphocytes of RA patients and normal, healthy controls.

However, the specification does not provide any working examples in which strong methylation of regions "A" or "B" of the DR3 gene promoter was observed in human synovial cells and synovial infiltrating lymphocytes of RA patients as compared to these regions in peripheral blood lymphocytes of RA patients and normal, healthy controls.

The specification does not provide any working examples in which the development of RA or likelihood of developing RA is determined in a non-human organisms by detecting strong methylation of the DR3 gene promoter in samples obtained from synovial cells or synovial infiltrating lymphocytes.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he

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scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the present application, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only that hypermethylation of region "C" of the DR3 gene promoter in samples of human synovial cells and synovial infiltrating lymphocytes is correlated with increased risk of RA, but does not teach that hypermethylation of regions "A" or "B" can be detected in that human synovial cells and synovial infiltrating lymphocytes as indicative of RA. Further, the specification does not teach a representative number of non-human organisms in which the DR3 gene promoter methylation levels are increased as predictive of the occurrence of RA. The specification also does not teach a representative number of alternative methods that can be used to indirectly confirm strong methylation of the DR3 gene promoter, but rather only teaches that the methylation status of the DR3 gene promoter can be predictably determined by assaying for the methylation of CpGs present in the promoter. In view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Priority

6. It is noted that Applicant cannot rely upon the foreign priority papers to overcome the following rejections because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 7-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Takami et al. (Arthritis and Rheumatism. September 2004. 50, page S671, Abstract 1796).

Takami teaches a method comprising comparing the methylation state of a DR3 gene promoter region obtained from synovial cells of a test human subject with the methylation state of a DR3 promoter region obtained from peripheral blood lymphocyte cells of the test human subject or from peripheral blood lymphocyte cells of a healthy human subject. Takami teaches that the DR3 promoter region between -180bp and +51bp was specifically hypermethylated in synovial cells of patients with RA and that hypermethylation of this region of the DR3 promoter may be important for the pathogenesis of RA. Takami teaches each of the method steps recited in the present claims and thereby anticipates the claimed invention. Further, it is noted that MPEP 211.02 states that “a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where

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the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone.” Also, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give “life, meaning and vitality” to the claim, “then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation”. In the present situation, the claim language of “for determining development of RA or the likelihood of developing RA” is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Accordingly, the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight.

Regarding claim 8, the method of Takami for determining the methylation state of the DR3 promoter further includes the steps of treating the DR3 gene promoter with sodium bisulfite which converts unmethylated cytosines to uracils in CpG sequences, amplifying DR3 gene promoter sequences by PCR using primers specific for methylated and unmethylated DR3 sequences, detecting the methylation state of the DR3 gene sequences, and confirming that the DR3 region consisting of nucleotides -180 to +51 obtained from the synovial cells is strongly methylated.

Regarding claims 9 and 10, the method of Takami concludes that the subject has developed RA when the DR3 promoter region obtained from the synovial cells is more strongly methylated than the DR3 promoter region from peripheral blood lymphocytes of healthy control subjects.

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8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Takami et al (25 November 2003; cited in the IDS of 8/25/06; see translation attached) teaches the results of a DNA methylation analysis of the DR3 promoter. Takami reports that allele-specific methylation occurred in the CpG region of 380-180bp upstream of the translation start site and that CpG regions downstream were unmethylated. It is stated that based on the methylation results, it is possible that DR3 may be subject to genomic imprinting and that future research will focus on studying the effect of methylation on RA. However, Takami does not specifically teach the methylation status of the DR3 gene promoter in DR3 nucleic acids obtained from synovial cells or synovial infiltrating lymphocytes and does not specifically teach that an increase in the methylation of the DR3 gene promoter in DR3 nucleic acids obtained from synovial cells or synovial infiltrating lymphocytes as compared to peripheral blood lymphocytes is indicative of risk of developing RA.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Carla Myers/

Primary Examiner, Art Unit 1634